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Ahead of the Curve

The Role of the Clinical and Translational Science Awards Program in Improving the Quality and Efficiency of Clinical Research

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Recognizing the need to increase the efficiency and quality of translating basic discovery into treatment and prevention strategies for patients and the public, the National Institutes of Health (NIH) announced the Clinical and Translational Science Awards (CTSAs) in 2006. Academic health centers that competed successfully for these awards agreed to work as a consortium and in cooperation with the NIH to improve the translation process by training the next generation of investigators to work in interdisciplinary teams, developing public-private partnerships in the movement of basic discovery to preclinical and clinical studies and trials, improving clinical research management, and engaging with communities to ensure their involvement in shaping research questions and in implementing research results. The CTSAs have addressed the crucial need to improve the quality and efficiency of clinical research by (1) providing training for clinical investigators and for bench researchers to facilitate their participation in the clinical and translational research environment, (2) developing more systematic approaches to clinical research management, and (3) engaging communities as active participants in the design and conduct of clinical research studies and trials and as leaders in implementing health advances that are of high importance to them. We provide an overview of the CTSA activities with attention to these three areas, which are essential to developing efficient clinical research efforts and effective implementation of research results on a national level. ***CHEST 2011; 140(3):764–767***

Abbreviations: AHC = academic health center; CER = comparative effectiveness research; CTSA = Clinical and Translational Science Award; IRB = institutional review board; NIH = National Institutes of Health

The doubling of the National Institutes of Health (NIH) budget in the new millennium, combined with the rapid acceleration in biomedical research discoveries, increased the urgency of translating laboratory results and proven medical advances into tangible, health-related outcomes. In 2006, after extensive consultation with stakeholders, the NIH, with Elias Zerhouni, MD, as the director, opened the Clinical and Translational Science Awards (CTSAs) program, a multiyear cooperative initiative designed to increase the efficiency of translation of research from the laboratory through the developmental pipeline into research in the clinic and then into the community in an iterative fashion. Currently, 60 funded academic health centers (AHCs) are actively engaged in the transformation of health-care research by improving the translation of research and discovery from laboratory to clinic and community and back again. Relevant information about the CTSAs can be found at the CTSA Consortium Web site, www.ctsaweb.org. The transformation includes the development of public-private partnerships, the educational preparation of the next generation of translational investigators, the improvement of clinical research management, the engagement of communities in a bidirectional dialog, and the establishment of informatics and communication tools that support a broad range of research activities. The CTSA institutions, with the leadership of the principal investigators and their teams, are developing regional and national consortia; participating

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in research networks; and sharing training programs, research resources, technology, expertise, best practices, software, and educational programs. Each CTSA site has an external advisory board that provides a multidisciplinary critique of its program. One of the major goals of the national CTSA consortium is to improve the quality, efficiency, and conduct of clinical research. To maximize its effectiveness, the consortium has developed national programs to (1) train new investigators in clinical research; (2) improve clinical research management with a focus on issues that have been historically difficult, such as protocol processing and activation, participant recruitment and retention, and contracts negotiation; and (3) develop effective strategies for community engagement. CTSA institutions have developed new informatics systems and technologies to assist in these endeavors; some are specific to the institutions and others have been shared widely across the CTSA consortium and with other institutions as well.

Training Investigators in Clinical and Translational Research

The CTSA initiative is predicated on the notion that clinical and translational science can advance most rapidly by providing investigators from a broad variety of disciplines the opportunity to train and then conduct clinical research in multidisciplinary teams. Each CTSA site provides funding for institutional pilot projects, which are open to investigators and interdisciplinary teams based on scientific value. Health professionals from schools of medicine, nursing, pharmacology, dentistry, nutrition, and physical therapy are joined by investigators from other disciplines, such as basic biosciences, engineering, physical sciences, and social sciences. The CTSAs have developed a robust curriculum to prepare this heterogeneous group for careers in clinical and translational research and to elevate the discipline to meet the demanding standards of current clinical investigation. For example, scholars learn to interact with and submit applications to the US Food and Drug Administration for investigational new drugs.

In developing the training programs, the CTSAs first performed a systematic inventory of required information, assembled a cadre of experts to serve as instructors, and then leveraged communication tools to meet the diverse needs of busy professionals. The consortium developed a Web-based repository of teaching instruments that could be accessed from all sites. Although many courses are open to all, junior investigators seeking to develop a career in clinical science are encouraged to obtain advanced degrees to document their comprehensive education and competence; research coordinators and other trainees are similarly certified. Many of the training programs have been recorded so that they can be made available to AHCs and other institutions that are not a part of the CTSA consortium, including those located in states without CTSAs that seek to strengthen their research efforts in clinical and translational science.

Developing a Systematic Approach to Clinical Research Management

In order to carry out the broad mandate of the CTSAs, the AHCs have created academic homes for clinical and translational research. Many of them have a staggering array of occupants; the larger centers have hundreds or even thousands of investigators who might either seek or wish to provide research resources; the resources include core laboratory services, expertise, technologies, instruments, special biologic materials, archived specimens, or other products of value to others. The provision of efficient and meaningful access to valuable resources without overwhelming the providers or leaving expectations unfulfilled because of funding limitations is a challenge to all principal investigators. One response has been the systematic development of Web-based accession systems, the cataloging of resources, and managed consultation services.

Another response has been the institution of project managers, also called "navigators" or "concierges," who assist investigators and triage requests based on needs assessments and funding sources. Those with the greatest needs, often investigators new to clinical and translational science, have been able to overcome major hurdles in the creation of a research plan and a protocol before it is submitted for scientific and institutional review board (IRB) review. Project managers are adept at drafting checklists and identifying pathways for the timely completion of tasks that are needed to characterize, identify, test, and develop a potential product to be used for the prevention, diagnosis, or management of disease. Often, these pathways involve contact with individuals who will become research partners; these include other basic science and clinical investigators and expert consultants in statistics, study design, informatics, and imaging.

Some CTSA programs have created project development teams that are composed of experts from a variety of disciplines, such as basic and clinical science, statistics, imaging, pharmacology, regulatory knowledge, ethics, and clinical trials conduct. It is the team's task to review proposals and suggest avenues of approach that hold potential promise for answering key questions, with the mutual goal of improving the

likelihood of developing a plan that will achieve its intended goals and attract funding support.

Industry, funding institutions, and members of the public, as well as investigators and research institutions, expect the CTSA initiative to improve the efficiency of conducting clinical trials at AHCs. The potentially devastating effect of inefficient management of clinical research was documented by process analysis of phase 3 oncology trials[1] in which investigators reported 110 processing steps at a single institution and the finding that fewer than one-third of those steps added value to the final protocol. In a subsequent study[2] of a national oncology group's Phase 3 clinical trials, it took an average of more than two years for the trials to open starting from the time the protocols were written.

To develop and implement standards for efficient trial activation, participating CTSA institutions have appointed a Champion of Change, often a dean or vice chancellor, an individual with authority to effect changes in the institution's clinical trials offices. The champions develop strategies, map processes, track performance, develop management teams, and evaluate the effects of implemented changes. Key to their effectiveness is the elimination of steps without value and the substitution of parallel or collective evaluation for tandem processing. The CTSA institutions have established a pattern of self-analysis, an awareness of the importance of achieving efficiency, and interactive networking, which has resulted in improvement in management at many of the sites.

A complete inventory of the process improvements at all sites has not yet been compiled. However, between 2006 and 2010, 15 sites developed process maps, and 20 of the first 46 sites reported process changes and improved performance. Several sites reduced processing times by $>30\%$. The CTSA sites differ markedly in their research portfolios, institutional governance, and management styles. Not unexpectedly, strategies for improvement differ as well. Some CTSA sites have developed alternative IRB review arrangements in response to the heavy load of protocol reviews and the concern that multiple IRB reviews add no established value.[3,4] These arrangements include contracts with external IRBs; reliance agreements with other institutions, in which partner sites agree to rely on each other's IRB approvals; federated IRBs; and common IRBs, in which participating institutions create an IRB in which they each share membership. Some of these arrangements were described in a presentation to the Secretary's Advisory Committee on Human Research Protections on October 19, 2010.[5]

In addition, new ways of encouraging enrollment in clinical trials are being developed in conjunction with efforts in community engagement and in development of "virtual" Web-based communities of potential participants. For example, Paul Harris, PhD, and his team at Vanderbilt University Medical Center in Nashville, Tennessee, have developed a Web-based program (www.ResearchMatch.org) that allows potential clinical trial participants to create a profile. The interested potential participants will then receive information about clinical trials relevant to them and can choose whether they wish to be contacted by the investigators conducting the trials. This informatics tool is now used nationally by >52 research institutions in 26 states.

Developing Effective Strategies for Community Engagement

Most CTSA sites have expanded programs for community engagement, which include cultural sensitivity training for researchers, community and provider education and outreach, development of software to facilitate the collaboration of community practitioners, and facilitation of two-way communication with diverse populations and community groups. Acting independently or as regional consortia, CTSA sites have developed new or improved partnerships with their communities predicated on the development of trust, ongoing involvement, and bidirectional control of the agenda for establishment of priorities, clinical investigation, and communication about research findings and best practices. The ultimate aim is to mobilize communities to (1) identify their own health needs and the role of AHCs in framing a response to those needs, (2) work with academic partners on the design of clinical trials to develop evidence-based practices, (3) act as leaders in communicating about health research and the implementation of new methods of managing health issues, and (4) work with AHCs to evaluate existing practices.[6] Partnerships exist at all levels, from the immediate community surrounding a CTSA-associated institution, to a county-, regional-, or state-wide program, to a network that includes multiple states, a section of the country, and/or other areas of the world. Communities may be defined by location, demographic or ethnic composition, a shared exposure, or a particular rare or common disease. Community members are linked with academic counterparts and with each other through new media and communication systems, such as teleconferencing. To ensure a comprehensive approach to community engagement, CTSA institutions involve social and behavioral experts and economists, as well as experts in communications, informatics, education, research design, epidemiology, statistics, and ethics. In building community engagement activities, CTSA institutions have developed a deeper understanding of the complex factors involved in forming community

relationships and in designing metrics for assessing health outcomes.

Opportunities for the Future

In addition to providing expanded resources to support clinical and translational science at AHCs, the CTSA investigators are exploring research opportunities to address specific health needs in collaboration with each other, with industrial partners, and with NIH-funded initiatives. Many CTSAs have developed productive relationships with their collocated Comprehensive Cancer Centers to leverage resources and to improve the efficiency of clinical research processes. Targeted areas of CTSA focus include drug development, imaging, sleep disorders, diabetes prevention, chronic lung disease, chronic heart failure, emergency medicine, sickle cell disease, pain management, mental health disorders, and drug addiction, as well as other areas in the neurosciences. As funding for comparative effectiveness research (CER) becomes available, the CTSA institutions have identified CER as a high priority; joined together to establish working groups with assigned tasks, such as the development of standards, definitions, and levels of evidence; and developed and enlarged training programs to prepare investigators to launch and conduct high-quality CER research.

Currently, the CTSA program, which is directed by the National Center for Research Resources of the NIH at a funding level of approximately $500 million annually, includes a total of 60 research institutions. Francis S. Collins, MD, PhD, the current NIH director, has proposed that the CTSAs form the backbone of a new NIH center, the National Center for Advancing Translational Sciences; this new center is anticipated to be established in fiscal year 2012. The mission of the National Center for Advancing Translational Sciences would be to advance the discipline of translational sciences and speed the development of new molecular entities for rare and neglected diseases. The strategic goals of the CTSA are well matched to those of the new center, because the sites are now involved in the development of efficient and effective process management, training programs, information sharing, and product-development pipelines. The two ends of the "translational" spectrum, from drug development to CER, might seem incongruent; however, the consortium includes institutions that are uniquely positioned to develop further leadership in these two ends of the spectrum. The future research activities in the CTSA institutions will be based, in large part, on opportunities developed and funded by the NIH. We anticipate that the synergies and the dynamism of the consortium that developed during the past 5 years will continue to accelerate the translational activities, beginning with discovery science and resulting in new treatment and prevention strategies for patients and communities.

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References

1. Dilts DM, Sandler AB. Invisible barriers to clinical trials: the impact of structural, infrastructural, and procedural barriers to opening oncology clinical trials. *J Clin Oncol*. 2006;24(28):4545-4552.
2. Dilts DM, Cheng SK, Crites JS, Sandler AB, Doroshow JH. Phase III clinical trial development: a process of chutes and ladders. *Clin Cancer Res*. 2010;16(22)5381-5389.
3. Grady C. Do IRBs protect human research participants? *JAMA*. 2010;304(10):1122-1123.
4. Millum J, Menikoff J. Streamlining ethical review. *Ann Intern Med*. 2010;153(10):655-657.
5. Mah E, Bierer B, Cobb N, Johnson T, Hirschfeld S. Secretary's Advisory Committee on Human Research Protections (SACHRP). Meeting Presentations. US Department of Health and Human Services Web site. http://www.hhs.gov/ohrp/sachrp/. Published October 19-20, 2010. Accessed March 14, 2011.
6. Michener JL, Yaggy S, Lyn M, et al. Improving the health of the community: Duke's experience with community engagement. *Acad Med*. 2008;83(4):408-413.